

Findings and Recommendations:  
**Sullivan Working Group on DAIDS Regulatory Activities**

**May 16, 2006**

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## EXECUTIVE SUMMARY

The Director of the National Institute of Allergy and Infectious Diseases (“NIAID”), National Institutes of Health (“NIH”), Anthony Fauci, M.D., organized the Sullivan Working Group on DAIDS Regulatory Activities to evaluate the structures and operations of the Division on AIDS (“DAIDS”) that are responsible for regulatory activities and processes. In fulfilling our charge, we met 13 times over a 7-month period. During this effort, we conducted over 60 interviews and received 6 presentations reaching the full range of the Division’s stakeholders, partners, constituents, and employees, as well as others knowledgeable about clinical trials.

We developed five general findings backed-up by several specific findings discussed in detail in the body of this report:

- 1. DAIDS personnel are highly motivated, committed, and hard working.**
- 2. Rapid program growth, complexity, and international expansion have been major contributors to tensions and operating inefficiencies.**
- 3. There have been important deficiencies in key areas of DAIDS management.**
- 4. DAIDS trials in resource-poor countries face important regulatory and ethics challenges not fully under DAIDS control and common to all sponsors.**
- 5. Effective resolution of these issues is time-sensitive. Resolution of certain of them requires urgent attention.**

Of these five general findings, three are the core focal points of this effort. The first is our finding that program growth, complexity, and international expansion have been dramatic over a relatively short period of time. But in the same period, growth of resources supporting DAIDS regulatory activities has not matched program expansion. As a result, regulatory activities have not met the needs of the programs. The lack of a common approach and documentation on policies, standards, and processes has exacerbated the impact of program growth and expansion. The new structures for trial networks and multi-trial sites being developed by DAIDS will also amplify the impact of program growth by requiring different and additional regulatory skills and resource deployment.

The second core focal point is our finding of deficiencies in key areas of DAIDS management. Deficiencies in DAIDS management have made the usual tension that occurs between the clinical mission and the role of regulatory activities highly disruptive and have undermined the effectiveness of regulatory activities.

The third focal point is our finding that DAIDS trials in resource-poor countries face challenges common to all sponsors. The application of United States’ regulatory, safety, and ethics requirements in clinical trials in resource-poor countries raises questions that remain unsettled for all funders and sponsors of trials. There is no apparent mechanism for DAIDS, NIAID, or the community of United States’ sponsors and funders of clinical trials conducted in resource-poor countries to discuss common challenges or explore common solutions.

We developed five general recommendations backed-up by several specific recommendations discussed in more detail in the body of this report:

- 1. Revise the organizational structure and authority for developing regulatory policies and overseeing regulatory activities.**

2. **Improve DAIDS and regulatory leadership.**
3. **Determine and achieve appropriate FTE levels and competencies for staff engaged in regulatory activities.**
4. **Facilitate the resolution of the common challenges of United States' sponsors and funders conducting clinical trials in resource-poor countries.**
5. **Take action to assure timely and effective implementation of these recommendations.**

## **BACKGROUND**

The Sullivan Working Group on DAIDS Regulatory Activities (the “Working Group”, “we”) was organized by the Director of the National Institute of Allergy and Infectious Diseases (“NIAID”), National Institutes of Health (“NIH”), Anthony Fauci, M.D., in August 2005, and convened in September 2005. It was created in response to external and internal adverse perceptions about how regulatory activities were being conducted within the Division on AIDS (“DAIDS” or the “Division”) and the adverse impact on effective and timely accomplishment of the DAIDS mission. It functioned as a working group of the NIAID Advisory Council (the “Advisory Council”) to advise the NIAID Director. Its purpose was to review regulatory processes at DAIDS and recommend improvements.

The Working Group was composed to assure both a high level of subject matter competence and independence. Dr. Fauci appointed the former United States Secretary of Health and Human Services, Louis W. Sullivan, M.D., as chair and six other members with expertise in human subject clinical research, distribution of therapeutics in resource-poor countries, international human subject research, bioethics, and food and drug law and regulations. In addition to the former Secretary, the Sullivan Working Group membership is listed below. Member biographical summaries are in the Appendix.

- **John D. Arras, Ph.D.**, Porterfield Professor of Biomedical Ethics and Professor of Philosophy, University of Virginia
- **Gail Cassell, Ph.D.**, Vice President for Scientific Affairs and Distinguished Lilly Research Scholar for Infectious Diseases at Eli Lilly and Company
- **Susan S. Ellenberg, Ph.D.**, Professor of Biostatistics, University of Pennsylvania Center for Clinical Epidemiology and Biostatistics; Associate Dean for Clinical Research in the School of Medicine
- **Maria Freire, Ph.D.**, Chief Executive Officer of the Global Alliance for TB Drug Development
- **Peter Barton Hutt, LL.B., LL.M.**, Senior Counsel, Covington & Burling
- **Gary Schoolnik, M.D.**, Professor of Medicine, Microbiology and Immunology, Stanford School of Medicine

The Sullivan Working Group was supported by Michael Calhoun, a health care management consultant and former Chief of Staff of the United States Department of Health and Human Services, who served as Senior Consultant (“Senior Consultant”).

The formal charge from the NIAID Director was to evaluate the following areas of the Division's regulatory activities:

- The current organizational structure for addressing DAIDS regulatory matters
- The roles and responsibilities of individuals within DAIDS involved in regulatory processes
- The existing standard operating procedures (both written and non-written) for carrying out the regulatory work of DAIDS
- The formal and informal channels for communication for dealing with regulatory matters within DAIDS, and between DAIDS and DAIDS-supported investigators
- The timeliness of completing critical functions

This evaluation was expected to take three to six months. The final report is to be submitted to the NIAID Director and the Advisory Council. The Working Group was requested to report to the NIAID Director if during this review a concern emerged regarding patient safety. No specific instance of a threat to patient safety was reported to us during our review.

## **APPROACH**

We engaged our charge in deliberations during 13 meetings that took place between September 2005 and April 2006. We solicited comments from a broad range of individuals and organizations in the federal government, the United States clinical trials community, and local people familiar with or involved in clinical trials in countries with limited resources and capability for supporting clinical trials ("resource-poor countries"). We reviewed documents, received presentations, and conducted interviews. We also received presentations from the Senior Consultant regarding his interviews and document reviews. The Working Group and the Senior Consultant conducted over 60 interviews. Interviewees and presenters represented a rich sampling of the full range of DAIDS stakeholders, partners, constituents, and employees and others knowledgeable about clinical trials, including the following:

- NIAID and DAIDS senior management
- Former DAIDS senior leadership and DAIDS regulatory leadership
- The current and past Director of the Office for Policy in Clinical Research Operations ("OPCRO")
- The Director of the DAIDS Regulatory Affairs Branch ("RAB") and the management team
- Officials at the Food and Drug Administration ("FDA"); Office for Human Research Protection ("OHRP"); the National Cancer Institute, National Institutes of Health; and the Centers for Disease Control and Prevention ("CDC")
- Staff members of the Senate Finance Committee
- Leaders of and investigators from the clinical trial networks conducting DAIDS clinical trials
- Investigators from resource-poor countries and investigators involved with clinical trial sites in resource-poor countries
- A senior leader of clinical trials in a large pharmaceutical company

We focused our review on those regulatory activities having a significant effect on DAIDS regulatory operations, protocol development, patient safety, human subject protection, and monitoring. During our review, it became clear that the activities of the Pharmaceutical Affairs and Clinical Research Resources Branches should not be within the scope of our efforts. The

responsibilities of these branches include a narrow range of regulatory responsibilities the execution of which was not identified in our review as being significantly problematic. While some process issues related to these units were brought to our attention, they were minor and largely attributable to these functions being under-staffed while managing large and complex responsibilities. Our findings and recommendations for achieving balance between regulatory resources and program scale will also be helpful to these functions. In addition, during our review we learned that many DAIDS standard operating procedures relating to regulatory requirements were incomplete or outdated and are being revised and updated by OPCRO. Consequently, we did not review existing DAIDS regulatory-related standing operating procedures.

Our fact-finding and deliberations were conducted with regard for confidentiality and protection of individual identity. In most cases, the Senior Consultant conducted interviews in strict confidence and reported aggregated views. In other cases, we received presentations and conducted interviews ourselves, providing assurances of confidentiality to participants. Our perception is that this approach earned the confidence and trust from interviewees and presenters, resulting in a comprehensive and candid information base for these findings and recommendations.

## **FINDINGS**

### **Overview**

We were impressed with the level of commitment of DAIDS staff involved in regulatory activities to assure safe clinical trials. But despite this commitment, we found that regulatory operations at DAIDS have been adversely affected primarily by five factors: rapid program growth, insufficient support resources relative to program growth, management deficiencies, inadequate organizational structure, and a lack of clarity about the application and interpretation of United States government requirements for clinical trials in resource-poor countries.

Based on our evaluation, we reached five general findings. Three of these findings identify the factors limiting effective regulatory operations at DAIDS and our best judgment about the root causes of the potential threat they pose. Another finding acknowledges the motivation and effort of DAIDS staff. We want to be sure that, despite the deficiencies identified in this report, it is understood that staff is serving the mission and organization with dedication and energy. The final finding reports our view of the urgency to address the three findings on DAIDS regulatory operations.

- 1. DAIDS personnel are highly motivated, committed, and hard working.**
- 2. Rapid program growth, complexity, and international expansion have been major contributors to tensions and operating inefficiencies within DAIDS.**
- 3. There have been important deficiencies in key areas of DAIDS management.**
- 4. DAIDS trials in resource-poor countries face important regulatory and ethics challenges not fully under DAIDS control and common to all sponsors.**
- 5. Effective resolution of these issues is time-sensitive. Resolution of certain of key issues requires urgent attention.**

The specific findings that back-up these general findings are provided below.

**Finding # 1: DAIDS personnel are highly motivated, committed, and hard working.**

For the DAIDS staff, seeking breakthroughs in the detection, treatment, and prevention of HIV/AIDS is a passion. Senior leadership, managers, and staff are highly motivated to achieve mission success. The scale of the AIDS epidemic, the enormity of its impact, and the role of DAIDS in helping to address it are well understood by staff, NIAID, and the external clinical trials community. Both within and outside of DAIDS, we found a uniformly strong sense of the urgency for developing effective treatments and prevention and an equally uniform recognition of the importance and leadership of the Division's programs in achieving success. Outside of DAIDS, there was also uniform acknowledgement of and respect for the high level of commitment and dedication of the entire DAIDS staff.

Among the indicators of staff's high level of motivation is their commitment to meeting program needs despite the significant effort needed to do so. In many instances, staff workloads are extraordinary. Because of their depth of commitment to the mission and for the reasons identified in our finding on program growth, DAIDS regulatory and program staffs labor under heavy program-driven workloads. Typically, staff regularly works extended hours to complete their tasks. Many staff members take on extra responsibilities to help address operating and policy challenges, adding further workload burden.

**Finding # 2: Rapid program growth, complexity, and international expansion have been major contributors to tensions and operating inefficiencies within DAIDS.**

The DAIDS human clinical trials program has grown dramatically in volume and complexity, including international expansion, in a relatively short period of time. The clinical trials program growth has outpaced the capacity of regulatory staff, straining the ability to provide the appropriate regulatory engagement. Expansion of international sites, especially in countries with limited resources for supporting trials, has had a disproportionate impact on regulatory activities. These consequences of program growth and expansion are exacerbated by the lack of common regulatory policies, processes, and documentation across DAIDS. The new network and site structures being developed by DAIDS will likely further exacerbate the effects of program growth and expansion on regulatory activities in DAIDS.

In particular, workload levels and program growth have limited the time available to staff to process protocols and develop and maintain current and consistent standards and standard operating procedures. It has also constrained the time available to staff to give more detailed, individualized focus to protocols and trials. Under these circumstances, it is not surprising that regulatory staff has often been deliberate and conservative in interpreting and applying requirements, especially for trials in countries not well equipped to support clinical trials. This cautious and protective approach has promoted regulatory policies and approaches that are sources of increased tension and friction between program and network staffs eager to address the pandemic, and regulatory staff beleaguered by growth and the setting of clinical trials and highly motivated to ensure the protection of patients and human subjects.

***Growth in the number and complexity of DAIDS protocols has been dramatic.***

The most significant overall growth occurred in the past five years, with the number of network trials nearly tripling since 2000.

	1996	2005
<b>Network protocols and studies*</b>	284	412
<b>Protocols/studies involving multiple drugs</b>	200	350
	2-3 drugs per trial	6+ drugs per trial

***Increase in the number of DAIDS international sites, mostly in resource-poor countries, has also been dramatic.***

Adding to program growth and complexity has been the expansion of the clinical trials program abroad. International expansion has been significant over the past 10 years, from 2 to over 750 international sites. The largest increase, over 450 additional international sites, has occurred in the past 5 years. Growth in resource-poor countries that host protocols has also been significant, from none to 22 in ten years, and doubling in the past 5 years.

	1996	2005
<b>International sites</b>	2	750+
<b>Countries hosting protocols</b>	3	47
<b>Resource-poor countries hosting protocols</b>	0	22

DAIDS leadership believes that, going forward, the number and size of international DAIDS trials, principally in countries with limited resources, will need to grow and become more complex. As detection tools, prevention, and treatment approaches improve, HIV/AIDS incidence will decline, so that larger population pools will be needed for trials. As survival rates increase, trials will become more complex because of the impact of the usual aging-related conditions (such as cardiac disease and diabetes) among patients with continuing HIV/AIDS symptoms.

***Resources supporting DAIDS regulatory activities have not matched program expansion.***

Growth in regulatory support for the clinical trials program has not kept pace with the rapid growth in program size and complexity. For example, within OPCRO, RAB has the leading role in regulatory activities. RAB employee FTE's increased from 5 to 8 in 2002. Since then, RAB employee FTEs have remained flat. Resource increases have been in contractors. In recent years, 5 RAB contractor FTEs have been added through the Henry Jackson Foundation arrangement. However, these contractors perform many, but not all, RAB regulatory functions. Through another arrangement, 15 contractors have also been added to perform administrative and routine functions and information technology services in support of RAB operations.

While increases in contractor support have helped to reduce some of the burden on DAIDS regulatory staff from clinical program growth, contractors are limited in both the scope of work they can perform and their decision-making authority. Therefore, regulatory tasks requiring DAIDS staff continue to increase despite contractor support. Furthermore, increased numbers of contractors require increased staff time to supervise them and their work, adding to the volume and complexity of the work of DAIDS regulatory staff.

Despite more contractors, the demands of program growth are also challenging contractor capability. For example, within OPCRO, the Clinical Research Resources Branch conducts the regulatory file reviews (monitoring) for DAIDS clinical trials. In 2001, 80 site contractors

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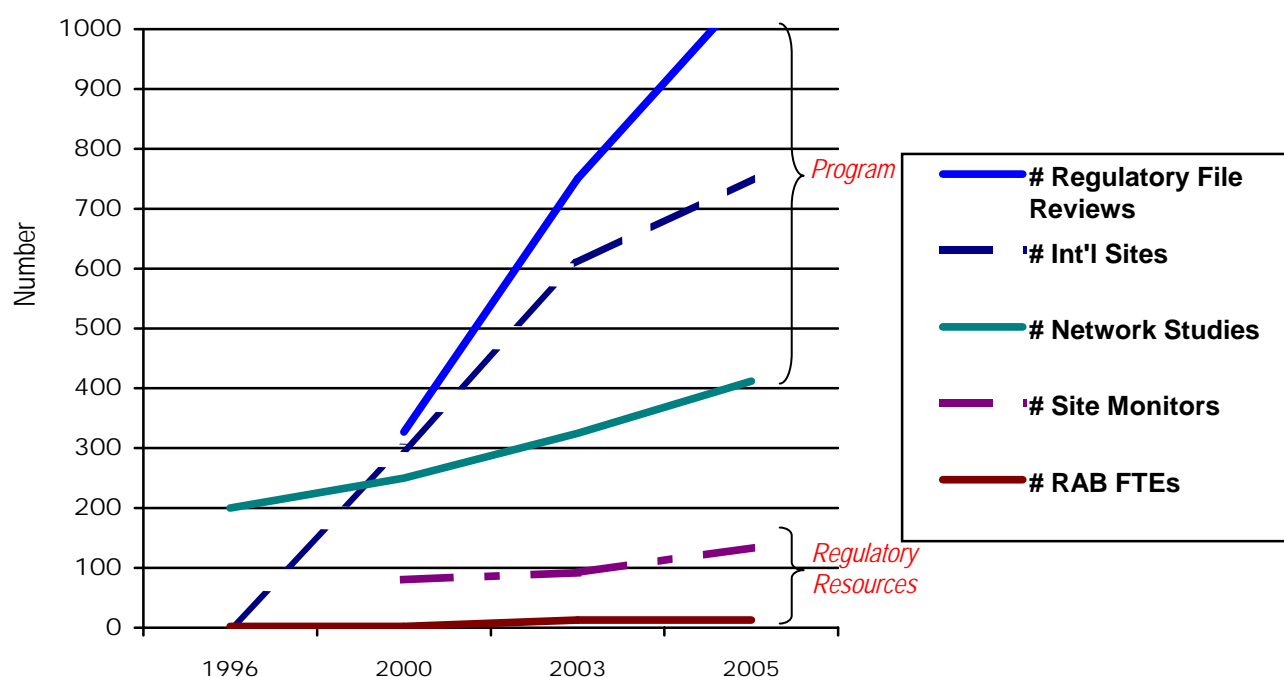
\* Data for non-network trials are not available, network trials are about 75% of total trials

conducted 327 regulatory file reviews. In 2005, 135 site contractors struggled to conduct 1017 reviews, a 67% increase in contractors versus a 311% increase in inspections.

	1996	2000	2001	2002	2003	2005
<b>RAB FTEs*</b>	2			8	13	13
DAIDS employees	2			8	8	8
Henry Jackson employees (performing many RAB regulatory activities)	0	0	0	0	5	5
<b>RAB support contractors*</b> (including support for IT transformation)	25					40
<b>Regulatory file reviews*</b>			327			1071
<b>Site monitoring contractors*</b>			80	87	92	134

As indicated in the chart below, the growth of the DAIDS program has significantly outpaced that of regulatory resources needed to support it.

**Comparison of Growth of Program and Regulatory Resources**



***As a result of these factors, regulatory activities have not fully met the needs and expectations of the programs and networks.***

While program expansion increases the volume of work across DAIDS generally, international expansion affects regulatory activities more acutely. There is uncertainty and lack of clarity and

\* Data from all years are not available

consensus regarding the regulatory processes and approaches that meet both United States government and local requirements and customs. Assuring safety and human subject protection, adverse event reporting, and pharmacovigilance are particularly complex in international trials, especially trials in resource-poor countries. Resolving issues of trial ethics can be highly complex and challenging in countries lacking adequate access to health care and having minimal government regulatory structures. These additional complexities and ambiguities require disproportionate effort and engagement of DAIDS regulatory staff in assuring that United States government regulatory requirements are met and that patients and human subjects are protected.

Because of the current role of regulatory activities in the protocol approval and oversight process, challenges to regulatory activities impede the trial process. DAIDS regulatory staff is less able to provide timely responses and have less time to explore the adequacy of more flexible interpretations, processes, and approaches.

***The lack of a common approach and documentation across DAIDS and NIAID regarding policies, standards, and processes for clinical trials has exacerbated the impact of program growth and expansion.***

As will be discussed, there is a lack of consistency in interpreting regulatory requirements and trial processes within DAIDS. In addition, there are regulatory issues that recur in most international trials in resource-poor countries, not only in AIDS-related trials, for which there is no significant guidance from NIAID or elsewhere. This lack of a common approach and guidance further burdens regulatory staff, which is already laboring under the effects of program growth and expansion. The absence of clear guidance and a common approach often leads DAIDS regulatory staff to assess these questions anew, each time they arise. This results in unnecessarily repetitive regulatory staff engagement, additional time to review and resolve, and inconsistent resolutions.

***The new network structure and multi-purpose sites being developed by DAIDS will require different and additional regulatory skills and resource deployment.***

DAIDS is in the process of reorganizing the clinical trial networks and sites, in part in response to the expansion of trials to international sites, especially those in resource-poor countries. Individual sites will support multiple protocols, and will function independent of networks. As currently envisioned, the networks will be re-organized around scientific areas of focus.

With this change in network and site structure, DAIDS will be required to have more uniform and transparent processes, standards, and policies. A DAIDS-wide mechanism will be needed to assure consistent application of regulatory policies and standards. DAIDS leadership will need to be more strongly engaged in directing and framing new and evolving regulatory roles and capabilities. At the current staffing levels and skill mix, these changes will further tax staff and intensify tensions between regulatory and program functions.

**Finding # 3: There have been important deficiencies in key areas of DAIDS management.**

In our view, the management deficiencies most adversely affecting regulatory activities are rooted in the tensions resulting from DAIDS leadership's and program leadership's passion for the clinical mission and from DAIDS regulatory management's vigilance in pursuing the role of regulatory activities in that mission. As a general matter in clinical trials, some tension between scientific program and regulatory functions is normal. In fact, this tension can be a constructive

force in achieving an appropriate balance between advancement of program goals and regulatory requirements, including patient safety and human subject protection. Successfully achieving a constructive balance typically varies with the extent to which regulatory activities are genuinely collaborative with, and well integrated into, program structure and execution, in contrast to being external and adversarial. The normal tension one finds elsewhere between program and regulatory has deteriorated at DAIDS and is not constructive. While recent controversies about specific DAIDS clinical trials and litigation pending at the time about DAIDS management practices have intensified this tension, they are not its cause. This tension has grown over time and has hindered program mission and working relationships.

The behaviors and practices among DAIDS leadership, program management, and regulatory management resulting from this disruptive tension have become hostile and adverse. They hinder achieving the DAIDS mission and are a significant impediment to effective program and regulatory operations. For its part, DAIDS leadership, over a number of years, has evidenced an under-appreciation of the role and importance of regulatory activities by not clearly defining its role and authority, not adequately embracing or enforcing its role and authority, and not effectively preventing or mediating the conflicts and disputes that typically arise over the interpretation and execution of regulatory requirements. As well, program leaders have been known to seek regulatory advice outside of internal regulatory structures.

In parallel, regulatory management over the years has evolved an “enforcement” role, rather than a collaborative and facilitative one that would help the program meet regulatory requirements and the protection of patients and human subjects. The regulatory function has taken on decision-making authority amidst the ambiguity about its formal role and empowerment. Increasingly, it has used this authority to be overly prescriptive and often adversarial. This approach has obstructed smooth and timely processes and has not advanced the effectiveness of DAIDS regulatory activities in protecting patients and human subjects.

***Deficiencies in DAIDS management have undermined the effectiveness of regulatory activities in support of the DAIDS mission.***

There has been no explicit requirement for consistency in trial processes and regulatory standards for DAIDS trials and no process to achieve this consistency. DAIDS-wide consistency is especially important because the disease focus is the same and the trial networks, sites, and many of the countries supporting the trials are common. Consistency greatly facilitates efficiency in regulatory effort and trial monitoring. It also facilitates better management of patient safety and human research protection. Nevertheless, many DAIDS standard operating procedures that would facilitate consistency are incomplete or outdated. Until most recently, key trial processes (i.e., Protocol Development, Site Establishment, and Monitoring) were conducted with varying degrees of consistency with, and oversight of, extramural policies and practices. OPCRO has recently launched a process to achieve greater consistency across DAIDS. It is largely a consensus-driven process rather than a clearly articulated mandate from senior leadership. Moreover, it is currently focused on only the 25% of DAIDS trials that are not conducted within DAIDS-related clinical trial networks. Focus on the 75% of DAIDS trials that are network-based is planned for later, but without clear time and outcome targets from DAIDS leadership.

Despite current efforts to establish more trial process consistency, there continues to be no mechanism, or clear plan to establish one, for regularly developing and overseeing uniform DAIDS-wide regulatory policies and processes. Similarly, there are no clear or uniform ethics policies and practice guidelines regarding the conduct of human clinical trials, nor plans to

establish them. The role and authority of regulatory activities in establishing policies and overseeing them continues to be poorly defined, thereby contributing to inefficiency and ambiguity. Recurring issues are too often re-addressed with each new protocol as matters of first impression and not always with consistency. Important policy and process issues are frequently addressed ad hoc. Standard operating procedures, which would significantly contribute to consistency and clarity, have been incomplete and irregularly updated.

In addition to an under appreciation of regulatory activities, DAIDS leadership has been slow with adequate responses to important regulatory challenges. OPCRO was created by the current DAIDS Director a few years ago with the goal of achieving more regulatory uniformity and better management of regulatory activities. But the effort faltered in the aftermath of the first OPCRO director's departure. Thereafter, the effort was slow to be resurrected due to several factors, including: caution on the part of DAIDS leadership because of ongoing "whistleblower" and EEO complaints; a sense of "intimidation" from perceived potential consequences of intervening too aggressively in regulatory matters; and DAIDS leadership's heavy focus on network re-organization and information technology infrastructure improvement. Despite these mitigating factors, we believe DAIDS leadership has been too slow to provide effective responses such as more clarity and structure in regulatory policymaking. Productive regulatory impact on trials and effective protocol approval processes and execution continue to be obstructed.

The Office of the DAIDS Director has recently re-engaged OPCRO in improving regulatory activities and developing a DAIDS-wide harmonization for common policies, processes and oversight. But the importance of the task and the priority it requires has not been sufficiently endorsed. For example, the direction and guidance given to this re-engagement has been neither clear nor forceful. The scope and content of the regulatory policies, trial processes, and trial ethics policies and practices that should be addressed by OPCRO have not been clearly laid out by the DAIDS leadership. There is no committed deadline for rolling out harmonization across the 75% of DAIDS trials that are conducted within trial networks. The harmonization effort currently has only a loose, consensus-driven target of the end of 2006. Progress and process seem constrained by the pace of the least willing program leader (or leaders), rather than driven by mandate and direction from DAIDS leadership. Finally, support for this effort is too often an after-hours, add-on task by staff rather than a priority assignment in lieu of other tasks.

Despite these challenges, the current OPCRO Director's several recent initiatives to improve regulatory processes and structures have been well focused and energetic. The effort could accrue even more positive results with stronger and more visible engagement and endorsement from DAIDS senior leadership. Compounding this situation at DAIDS, there is no significant guidance on principles and expectations on these issues from NIAID. Until very recently, NIAID has not had an established mechanism to identify and capture best practices in regulatory functions and to establish or compel harmonization across the divisions. NIAID-level direction is important not only for assuring a consistent and appropriate level of regulatory interpretation and application. It would also help relieve some of the burden on DAIDS (and other division) staff to assess and resolve issues that are common both to AIDS and non-AIDS trials, especially in the international arena. Such centralized coordination of policies and practices could also offer cost efficiencies by reducing duplication of effort among the divisions.

***Deficiencies in regulatory management have undermined the effectiveness of regulatory activities in support of the DAIDS mission.***

The management of regulatory activities has undermined the effectiveness of RAB in two critical ways. The role has been an enforcement rather than consultative one, and the approach has

been prescriptive rather than collaborative. The regulatory staff has evolved this role and approach due to several factors including:

- (1) Historical ambiguity about RAB's role and authority, and ambiguity about OPCRO's role and authority at its initiation
- (2) The decision by RAB leadership to adopt an unduly restrictive approach to FDA submissions
- (3) Signature authority for investigative new drug applications residing solely with RAB
- (4) Program expansion and the insufficient resources available to perform regulatory activities

Regulatory functions appear to have been prescriptive and insufficiently collegial and collaborative. Frequently this approach has impeded rather than facilitated the process of trial approval and launch. Often regulatory inputs are "late-in-process" interventions that contribute to delays and frictions.

The chosen role and approach of RAB leadership have reduced RAB's effectiveness in supporting the clinical mission and have frequently slowed or disrupted the trial approval and launch processes. Program staff and leadership insufficiently seek RAB's involvement. They often avoid encounters or otherwise seek alternative processes and channels, when possible, for addressing regulatory matters. Because of this role and approach, RAB attracts very strong criticism, not just from program staff, but also across the full range of DAIDS extramural investigators and networks. Finally, this role and style have required DAIDS senior managers to direct a disproportionate level of attention and time in mediating RAB actions and its consequences.

**Finding # 4: DAIDS trials in resource-poor countries face important regulatory and ethics challenges not fully under DAIDS control and common to all sponsors.**

Ambiguity about how to interpret and apply United States government regulatory, safety, and ethics requirements in resource-poor country clinical trials has been an important source of tension between regulatory and program staffs. It has also been an important focal point of DAIDS regulatory resources. However, DAIDS is not alone among sponsors or funders of clinical trials in resource-poor countries in confronting this challenge. It is a challenge increasingly shared across the human clinical trials community in the United States. For example, federal support for international trials increased nearly tenfold between 1994 and 2004, from \$78 million to \$705 million and the fastest growing share was for trials in resource-poor countries. The resolution of many of the challenges this large and growing proportion of trials represents remains unsettled.

Despite effective implementation of the recommendations offered in this report, sustained relief from this challenge is beyond the best efforts of NIAID, DAIDS, and the Office of Human Research Protections. A consensus among the broader community of United States' sponsors and funders of clinical trials in resource-poor countries is needed.

***The application of United States government regulatory, safety, and ethics requirements in resource-poor country clinical trials raises questions that remain unsettled and is a challenge shared across the United States' clinical trials community.***

There are at least five areas with recurring questions on how best to confront regulatory and trial-conduct functions that recur in DAIDS trials, particularly those in resource-poor countries:

- (1) Ethics Committees/Internal Review Boards: How best to address variations in the competencies of local committees, and manage conflicts among multiple layers of committees.
- (2) Differing cultural/social traditions: How best to accommodate human subject protection and safety requirements with local custom and practice, and manage the differing roles/status of women and children.
- (3) Informed consent: How best to achieve actual informed consent consistent with United States government requirements other than the use of long and complex forms common in United States-based clinical trials. How best to evaluate the validity of consent where education and access to health care is limited.
- (4) Access to care: How best to balance the goal of research with ethical questions regarding access to care for those precluded from the trial; how and how long to provide access for patients who seroconvert during trial and for other illnesses that arise; how and how long to provide access for participants post-trial.
- (5) When to require investigational new drug filings (INDs): What are appropriate interpretative guidelines for determining when INDs will be required for trials in foreign countries and when to require them even if not explicitly required by regulation.

***There is no apparent mechanism for DAIDS, NIAID or the community of United States' sponsors of clinical trials conducted in resource-poor countries to discuss common challenges or explore common solutions.***

Despite useful attempts at providing guidance by the Office of Human Research Protections, other United States government agency sponsors, foundations, industry, academia and other sponsors of trials have not reached common positions on these issues. So far as we have been able to determine, there is no ongoing forum or process in the United States for exploring common ground and seeking consensus.

**Finding # 5: Effective resolution of these issues is time-sensitive. The resolution of certain of them requires urgent attention.**

We believe resolution of the issues raised here are of the highest importance. Delay in effective resolution of these challenges will continue if not worsen current tensions, increase the incidence of avoidable delays in regulatory functions and protocol approval, increase the incidence of avoidable confusion in the conduct of ongoing and new trials, particularly international trials. Absent timely resolution, these challenges confronting DAIDS regulatory activities will intensify.

In recognition of the already significant demands on time, we believe some deficiencies have a higher potential for continued or intensified near-term disruption and safety risk. Addressing these challenges can and should be prioritized. In our view, the following deficiencies have a particularly high potential for continued or intensified disruption and near-term safety risks; they require high-priority attention:

- (1) DAIDS and regulatory management deficiencies
- (2) The lack of DAIDS-wide consistency in policies and procedures
- (3) The absence of a fully empowered mechanism for oversight and review at the DAIDS level
- (4) The lack of compulsory NIAID-level principles and guidance on key issues that cut across all divisions

## RECOMMENDATIONS

### Overview

Effective remediation of the current challenges confronting DAIDS regulatory activities is essential for sustaining patient safety and protecting human subjects, achieving program success, and improving both operating efficiency and staff morale. We offer five general recommendations for remediation of the challenges we have identified. The first three recommendations detail our view on the most important actions that are necessary for improving DAIDS regulatory operations: new regulatory structures, improved leadership, and resources that are better aligned with program size and future direction. The fourth recommendation presents our view on how best to resolve the broader challenge, which is beyond DAIDS' sole authority, of the appropriate interpretation and application of United States government requirements to clinical trials in resource-poor countries. Our final recommendation is guidance for prioritizing the implementation effort and how best to assure timely, practical implementation.

Within these five general recommendations, we provide details for achieving effective remediation. In aggregate, we are proposing 13 detailed actions focused on changes that address our view of both the key underlying drivers of the challenges in regulatory operations and those with the highest potential for yielding more effective and efficient regulatory activities.

Our five general recommendations are as follows:

- 1. DAIDS and NIAID should revise the organizational structure and authority for developing regulatory policies and overseeing regulatory activities.**
- 2. Improve the DAIDS and regulatory leadership.**
- 3. Determine and achieve appropriate FTE levels and competencies for staff engaged in regulatory activities.**
- 4. Facilitate the resolution of the common challenges of United States' sponsors and funders conducting clinical trials in resource-poor countries.**
- 5. Take action to assure timely and effective implementation of these recommendations.**

**Recommendation #1: DAIDS and NIAID should revise the organizational structure and authority for developing regulatory policies and overseeing regulatory activities.**

Achieving clarity and consistency in regulatory policies and practices across DAIDS is one of the most important requirements for effective regulatory operations. It is also a crucial requirement for improved management of the patient safety and human subject protection risks associated with the DAIDS clinical trials program. We believe the most important action to be taken in improving DAIDS regulatory processes and in protecting patients and trial subjects is to strengthen the structures that oversee DAIDS regulatory processes and the authority for doing so. To some extent, this means clarifying roles, responsibilities, and authority. But it also means creating new structures, responsibilities, and authority.

We recommend four specific actions for improving the structure and authority of regulatory activities: strengthen regulatory coordination at the NIAID level; broaden and strengthen the DAIDS harmonization effort currently underway; restructure OPCRO and clarify its mandate; restructure RAB; and create a DAIDS-wide panel for policy-setting and dispute resolution regarding the conduct of clinical trials.

***Coordinate regulatory activities at the NIAID level in one of two alternative ways: centralization of regulatory activities or oversight by a director-level coordinating committee.***

We believe that coordination of regulatory activities across NIAID is important to assuring more effective and efficient regulatory operations at DAIDS. NIAID-level coordination would help to reduce the tensions and distractions of recurring interpretive conflicts, conserve regulatory resources at DAIDS and across NIAID as well, and help to ensure that appropriate standards for clinical trials are being established. Essential to effective NIAID-level coordination, no matter how it is approached, is requiring compliance with NIAID guidance and final decisions.

NIAID should establish for itself a clear and strong role in assuring consistency in key areas of trial conduct. It should strengthen consistency in the interpretation and execution of regulatory and trial requirements by undertaking the following:

- (1) Providing written guidance on NIAID-wide principles and standards regarding key trial-related issues common to all divisions
- (2) Requiring compliance with NIAID-wide guidance
- (3) Reviewing division compliance with NIAID-wide guidance

We offer two alternatives for implementing NIAID-level regulatory coordination:

***OPTION # 1***

Change the current division-based regulatory structure and centralize at the NIAID level, under a deputy director, overall authority and oversight of regulatory functions for all NIAID divisions. In creating the central control structure, determine the functions that would reside at the NIAID-level, such as patient safety, human subject protection, and clinical trial agreements, and those that would remain at the division level, such as daily advice on regulatory issues. Develop a structure and process for assuring NIAID-level control, but allowing for appropriate flexibility in division-level implementation. To enable the goal of consistency across NIAID and assure

appropriate levels of service for regulatory activities, regulatory staff at the division levels should be accountable to both the NIAID deputy director and the division director.

## **OPTION # 2**

Retain the current division-based regulatory structure, but empower an NIAID deputy director to coordinate and oversee regulatory activities by organizing and chairing a NIAID-wide regulatory coordinating committee. This regulatory coordinating committee would assure NIAID-wide consistency in regulatory principles and activities. While regulatory functions would remain within the divisions, they would be governed by NIAID guidance. Division-level regulatory activities would be subject to review by the designated deputy director and the committee. The committee would be comprised of the regulatory leaders from each division, meet regularly, and collaborate with the deputy director in assuring NIAID-wide consistency in regulatory activities.

### ***Broaden the scope and strengthen the mandate for timely completion of the current DAIDS-wide harmonization of trial policies and processes.***

In addition to the coordination of regulatory policy at the NIAID level, harmonization of clinical trial policies and processes across DAIDS is among the highest priority requirements for improved regulatory activities. It is also important for improving working relationships between regulatory and program staffs and making more efficient use of both program and regulatory resources. The current effort underway, led by the OPCRO Director, to harmonize policies and processes of some of DAIDS trials is a good start. Harmonization across all of DAIDS clinical trials is essential and needs to be among the highest priorities for implementation of these recommendations irrespective of the option selected for NIAID regulatory coordination.

In support of achieving the most appropriate level of harmonization, we recommend the following courses of actions. First, expand DAIDS-wide harmonization of trial policies and processes. Clarify the current project's scope to include all network trials and the major clinical trial components, protocol development, site establishment, and monitoring. Clarify policies and processes regarding the role and expectations of regulatory activities, authority for OPCRO harmonization efforts, and effective management of important and recurring issues such as trial ethics and processes. Second, mandate timely completion of the harmonization project for network trials. Make the current consensus-based end-of-year goal a firm target. Determine if the expansion of project scope described above can reasonably be achieved by the end of the year. Otherwise, establish an appropriate near term goal for completion.

### ***Strengthen the entire OPCRO operation by formalizing its authority.***

OPCRO has an essential role in improving and sustaining effective and efficient DAIDS regulatory activities over the long term. While it is currently on a promising course for fulfilling this crucial role, OPCRO would be more successful and timely in fulfilling this role if it were more clearly empowered so that its actions and statements carried uniformly recognized authority.

We believe that capturing the most value from a further empowered and strengthened OPCRO requires two additional actions: making the regulatory activities within RAB less adversarial and more supportive of and accessible to program staff and activities, and creating separate function areas from some activities now addressed by an overburdened RAB staff. Implementing these two actions will require two different approaches. Making regulatory activities less adversarial is a challenge of leadership and management. Appropriate redistribution of some RAB's responsibilities is a rather straightforward task, but will need assessment.

First, redefine the role of regulatory staff to be collaborators and facilitators, not decision makers. Establish performance requirements for all OPCRO function areas, including standards for collaboration, consultation, and facilitation; service to programs, and support of and cooperation with the mechanism recommended below for policy-setting and policy oversight of trial conduct. Consistent with the new service and collaboration expectations for regulatory activities, determine where and who in DAIDS should have responsibility for signing INDs and approving protocols.

Empower OPCRO with explicit authority to develop, implement, and maintain DAIDS-wide policies, standards, and procedures. Empower it to support effectively and assist in implementing policies, standards, and procedures. Give it adequate authority to require and deliver DAIDS-wide regulatory training programs. Provide OPCRO with additional FTEs and a skill mix appropriate to meet its responsibilities effectively.

Reorganize OPCRO consistent with best practices in clinical trial regulatory activities. Add appropriate new functions including a deputy responsible for day-to-day administrative operations. Determine the appropriate locations within OPCRO for two distinct new functions: conducting pharmacovigilance and developing and overseeing regulatory interpretation and policy. Move from within RAB to another area within OPCRO the responsibility for negotiation and oversight of clinical trial agreements, memoranda of understandings, and other agreements (if not performed at the NIAID-level).

Finally, reposition RAB to have a more effective impact on patient safety and human subject protection. The goal of this repositioning is for RAB to be more embedded in the program, become a sought after member of the team, and to have its impact to be more organic to the clinical trial process rather than being an enforcement barrier. This repositioning should result in RAB having a more robust impact on patient safety and human subject protection, to the extent that role is not performed at the NIAID-level as described in the options above. To help achieve this repositioning, define RAB's role as consultative and advisory. Consistent with its advisory and consultative role, move its current responsibility for clinical trial and other agreements to the OPCRO level as described above. Reassign its current IND signature authority, placing the authority where it is determined to be most appropriate.

***Create a DAIDS mechanism for policy-setting and regular policy oversight of the conduct of clinical trials.***

Another high priority requirement for DAIDS is a properly empowered, inclusive, and transparent mechanism for setting and overseeing DAIDS-wide policies governing regulatory activities, and ideally the full scope of the conduct of clinical trials. This committee should have final decision-making authority subject to review at the NIAID level, consistent with the option selected for NIAID-level coordination.

Irrespective of the option selected for NIAID-level coordination, the value of such a DAIDS mechanism would be increased consistency and higher quality not only in the interpretation and application of regulatory requirements, but also in the conduct of DAIDS clinical trials overall. It would provide an open and disciplined process for reconciling interpretive ambiguities and differences about regulatory and other trial conduct requirements. An additional and significant benefit of such a mechanism would be to enable the transition of RAB from being an enforcer to a collaborator. This would strengthen its impact, improve working relationships, and reduce tensions between regulatory and program functions.

We envision this mechanism as a committee composed of key DAIDS functions, with specific representatives present based on the subject matter at issue. It would not replace program or regulatory reporting relationships nor intervene in ongoing operations. It would have fundamentally two roles: first, setting policies governing regulatory activities and the conduct of clinical trials, including providing guidance to OPCRO in developing regulatory policies and overseeing regulatory requirements; and second, resolving ambiguities and disputes regarding the interpretation and application of regulatory requirements of clinical trial conduct requirements.

**Recommendation # 2: Improve DAIDS and regulatory leadership.**

Improving the way in which regulatory activities at DAIDS are managed is of critical importance to improving regulatory operations, limiting risk exposure for trial participants and DAIDS itself, and to effectively and efficiently achieving the Division's mission. We consider this recommendation to be among the most important priorities for timely implementation. We offer two specific actions for improving DAIDS and regulatory leadership.

***Make appropriate changes in DAIDS leadership and regulatory leadership in order to improve the effectiveness of regulatory activities.***

***Clarify and strengthen performance expectations in support of improved leadership of DAIDS regulatory activities.***

Performance criteria at the DAIDS Director level should include setting direction and policies, consistent with these recommendations, for the role and expectations of regulatory activities and for providing ongoing direction in the interpretation and implementation of regulatory requirements. Near-term specific examples would include defining explicit authority and providing clear endorsement for the OPCRO harmonization efforts and timeline. It would also include establishing policies and guidance for resolving, within DAIDS, the key recurring issues and questions arising both in the clinical trial process and in the interpretation and implementation of regulatory and other requirements, trial ethics, and human subject protection. Performance criteria at the DAIDS Director level would also include assuring genuine cooperation and collaboration across programs and between programs and regulatory activities and assuring a respectful workplace.

Performance criteria at the RAB Branch Chief level would include providing genuine support of the clinical program in meeting regulatory requirements and protecting patients and human subjects. It would also include maintaining cooperative, collegial, and positive relations with the clinical programs and engaging in collaborative problem-solving. The final criterion would be to perform in a consultative rather than decision-making capacity.

**Recommendation # 3: Determine and achieve appropriate FTE levels and competencies for staff engaged in regulatory activities.**

Irrespective of the option chosen for NIAID coordination, we believe that additional regulatory staff is needed to support more effectively the large and complex DAIDS clinical program. But merely adding staff will not be sufficient. Strengthening and realigning staff skills will also be necessary to meet the newly defined regulatory roles and responsibilities we recommend and the requirements of the new DAIDS trial network and site structures. Better aligning staff skills and performance with the evolving DAIDS clinical program is important. We believe it is

important to strengthen guidelines relating to and defining expectations of contract staff supporting regulatory activities.

**Recommendation # 4: Facilitate the resolution of the common challenges of United States' sponsors and funders conducting clinical trials in resource-poor countries.**

DAIDS clinical trials in resource-poor countries face important regulatory and ethics challenges, not fully under DAIDS' control and common to all sponsors. Therefore, DAIDS has limited influence over an important portion of its regulatory challenges. A solely internal approach to making DAIDS regulatory operations more effective and efficient has inherent limitations. Rising to the challenge of these issues is not limited to DAIDS regulatory and program activities, but applies also to other divisions within NIAID, across NIH, and to the broader clinical trials community as well.

There are ongoing efforts by international organizations to achieve formalized and technical agreements on certain issues attending clinical trials in resource-poor countries. This process is slow-moving and lacks significant impact. Informal consensus among United States sponsors and funders on critical operational issues can be reached in a more timely and practical fashion. It can have significant impact on a large portion of resource-poor country trials.

***NIH, NIAID, and others should convene a national forum of sponsors and funders of clinical research in resource-poor countries.***

Having a national mechanism for sharing views and approaches to common challenges, at the least, will facilitate convergence in practices and lead, over time, to standards and expectations about common behaviors. The value to both DAIDS and resource-poor countries would be significant as measured in time and resources saved from repeatedly seeking resolution with each new trial. There would also be significant value from shared approaches to trials that are more responsive, thoughtful, and balanced.

Because these challenges are shared across NIAID and NIH, and given their national stature, NIAID and/or NIH should take the lead in facilitating the launch of a mechanism for national consensus building. In particular, NIH and NIAID should invite other United States' sponsors and funders of clinical trials in resource-poor countries to support and convene a national forum on these issues. Other participants should include other United States government entities, pharmaceutical companies, and foundations. Participants should also include appropriate representatives from host countries of U.S.-sponsored clinical trials.

***Establish consistent NIAID-wide guidance regarding important or recurring issues that arise with trials in resource-poor countries and require compliance.***

Notwithstanding the national action recommended, DAIDS would be well served, as would other divisions, by NIAID establishing guidance and requiring compliance by all divisions. As a practical matter, this means two important changes in NIAID's current harmonization effort: making the results of the effort mandatory and broadening the effort to include the leading and most challenging issues that recur in resource-poor country trials.

***Develop DAIDS-wide policies and procedures regarding important or recurring issues that arise with trials in resource-poor countries.***

The value to DAIDS of this recommendation is the clarifying requirements that will be produced. Our previous recommendations urge establishment of mechanisms and processes for implementing DAIDS-wide regulatory policies and procedures. DAIDS policies and procedures implementing guidance from the actions under this recommendation should be integrated into the NIAID and DAIDS mechanisms and processes previously recommended.

**Recommendation # 5: Take action to assure timely and effective implementation of these recommendations.**

This recommendation is in response to our finding that effective resolution of these issues is time-sensitive and that resolution of some of them requires urgent attention. We have acknowledged efforts at both DAIDS and NIAID that are already attempting to address some of the issues we have identified.

We strongly believe that timely response to the challenges confronting DAIDS regulatory operations is of great importance. Resolution of some of the issues, in fact, requires urgent resolution. This sense of urgency is based on the importance of the DAIDS mission, the potential risk for further difficulties in DAIDS trials from continuation of the current state, and on the need to improve regulatory operations in advance of the new network and site structures.

# Appendix

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## Biographical Summaries of the Sullivan Working Group Members

**The Honorable Louis W. Sullivan** was the founding Dean and first President of Morehouse School of Medicine (MSM) in 1975. With the exception of his tenure as Secretary of the U.S. Department of Health and Human Services (HHS) from 1989 to 1993, Dr. Sullivan was President of MSM for more than two decades. On July 1, 2002, he retired from the presidency, but continues to support MSM, assisting in national fund-raising activities on behalf of the school. A native of Atlanta, Dr. Sullivan graduated magna cum laude from Morehouse College in 1954, and earned his medical degree, cum laude, from Boston University School of Medicine in 1958. He is certified in internal medicine and hematology. Dr. Sullivan was instructor of medicine at Harvard Medical School from 1963-64, and assistant professor of medicine at Seton Hall College of Medicine from 1964-65. In 1966, he became co-director of hematology at Boston University Medical Center and, a year later, founded the Boston University Hematology Service at Boston City Hospital. Dr. Sullivan joined the Boston University School of Medicine in 1966 and remained until 1975, holding positions as assistant professor of medicine, associate professor of medicine, and professor of medicine.

In 1989 Dr. Sullivan accepted an appointment by President George H.W. Bush to head HHS. Dr. Sullivan managed this federal agency responsible for the major health, welfare, food and drug safety, medical research and income security programs serving the American people. In January 1993, he returned to MSM as president. Dr. Sullivan is Chairman of the board of the National Health Museum in Washington, D.C. and is Chairman of the Sullivan Alliance on Diversity in the Healthcare Workforce. He also serves as Chair of the President's Commission on Historically Black Colleges and Universities, and is Co-Chair of the President's Commission on HIV and AIDS.

**John D. Arras** is the Porterfield Professor of Biomedical Ethics and Professor of Philosophy at the University of Virginia, where he directs the Undergraduate Program in Bioethics. He also teaches in UVA's interdisciplinary MA program in bioethics, and is affiliated with the Center for Biomedical Ethics in the Medical School. His most recent research interests include: assisted suicide, public health ethics, research on human subjects, international research ethics, theories of global justice and the social determinants of health, and methods of ethics. He is currently completing a book (tentative title: "Curb Your Enthusiasm: Skeptical Reflections on Method in Bioethics"). The author of scores of articles in bioethics, Arras is also co-editor of *Ethical and Regulatory Aspects of Human Subjects Research* (Hopkins, 2003); *Ethical Issues in Modern Medicine*, 6th ed. (McGraw-Hill, 2002); and *Bringing the Hospital Home* (Hopkins, 1995). Professor Arras is a longtime Fellow and former Board member of the Hastings Center, the nation's preeminent research institute in bioethics. He also consults regularly at the National Institutes of Health (NIH) in Bethesda, MD, and serves as a member of the ethics advisory board of the Centers for Disease Control and Prevention (CDC) in Atlanta. His work for the CDC currently focuses on vaccine policy and preparedness for a predicted world pandemic of avian influenza. Prior to his move to Virginia in 1995, Arras was for 14 years Associate Professor of Bioethics at the Albert Einstein College of Medicine Montefiore Medical Center, and adjunct Associate Professor of Philosophy at Barnard College/Columbia University. In 2006, Arras

received an Outstanding Faculty Award from the Virginia State Council of Higher Education.

**Gail H. Cassell** is currently Vice President, Scientific Affairs and Distinguished Lilly Research Scholar for Infectious Diseases, Eli Lilly and Company in Indianapolis, Indiana. She is the former Charles H. McCauley Professor and Chairman of the Department of Microbiology at the University of Alabama Schools of Medicine and Dentistry at Birmingham, a department that ranked first in research funding from the National Institutes of Health during the decade of her leadership. She obtained her B.S. from the University of Alabama in Tuscaloosa and in 1993 was selected as one of the top 31 female graduates of the 20th century. She obtained her Ph.D. in Microbiology from the University of Alabama at Birmingham and was selected as its 2003 Distinguished Alumnus.

She is a past President of the American Society for Microbiology (the oldest and single largest life sciences organization with a membership of over 42,000). She was a member of the National Institutes of Health Director's Advisory Committee and a member of the Advisory Council of the National Institute of Allergy and Infectious Diseases of NIH. She was named to the original Board of Scientific Councilors of the Center for Infectious Diseases, Centers for Disease Control and served as Chair of the Board. She recently served a three-year term on the Advisory Board of the Director of the Centers for Disease Control and as a member of the Secretary of Health and Human Services Advisory Council of Public Health Preparedness. Currently she is a member of the Science Board of the Federal Food and Drug Administration.

Since 1996 she has been a member of the U.S.-Japan Cooperative Medical Science Program responsible for advising the respective governments on joint research agendas, (U.S. State Department/Japan Ministry of Foreign Affairs). She has served on several editorial boards of scientific journals and has authored over 250 articles and book chapters. Dr. Cassell has received national and international awards and an honorary degree for her research in infectious diseases. She is a member of the Institute of Medicine of the National Academy of Sciences and is currently serving a 3-year term on the IOM Council, the governing board.

Dr. Cassell has been intimately involved in establishment of science policy and legislation related to biomedical research and public health. For nine years she was chairman of the Public and Scientific Affairs Board of the American Society for Microbiology; has served as an advisor on infectious diseases and indirect costs of research to the White House Office of Science and Technology Policy, and has been an invited participant in numerous Congressional hearings and briefings related to infectious diseases, anti-microbial resistance, and biomedical research. Currently she is a member of the Board of Directors of the Burroughs Wellcome Fund, the Board of (and Executive Committee of the Board) Research!America, the Leadership Council of the School of Public Health of Harvard University, and the Advisory Council of the School of Nursing of Johns Hopkins.

**Susan Ellenberg** is Professor of Biostatistics, Center for Clinical Epidemiology and Biostatistics, and Associate Dean for Clinical Research, University of Pennsylvania School of Medicine. From 1993 to 2004 she served as Director, Office of Biostatistics and Epidemiology in the Center for Biologics Evaluation and Research (CBER) at the

U.S. Food and Drug Administration; prior to that she served as the first Chief of the Biostatistics Research Branch in the Division of AIDS, National Institute of Allergy and Infectious Diseases (1988-1993), and served in the Biometric Research Branch in the Cancer Therapy Evaluation Program, National Cancer Institute (1982-1988). During Dr. Ellenberg's tenure at FDA she played a leading role in the development of international standards for design and analysis of clinical trials performed by the pharmaceutical industry, developed productive programs for post-marketing safety surveillance of biological products, and coordinated the development of policy for the establishment and operation of clinical trial data monitoring committees.

Dr. Ellenberg's research has focused on practical problems in designing, conducting and analyzing data from clinical trials. She has published extensively in both statistical and medical journals, on topics including surrogate endpoints, data monitoring committees, clinical trial designs, adverse event monitoring, vaccine safety and special issues in cancer and AIDS trials. She is a Fellow of the American Statistical Association and the American Association for the Advancement of Science, and is an elected member of the International Statistical Institute. Her book, *Data Monitoring Committees in Clinical Trials: a Practical Perspective*, co-authored with Drs. Thomas Fleming and David DeMets, was named Wiley Europe Statistics Book of the Year for 2002.

**Maria C. Freire** is President and CEO of The Global Alliance for TB Drug Development, a position she has held since 2001. During this time, the Alliance has built the largest pipeline of TB drugs in the world, advanced compounds into clinical testing and pioneered precedent-setting agreements with industry.

From 1995 to 2001, Dr. Freire directed the Office of Technology Transfer at the U.S. National Institutes of Health, where she was responsible for the central development and implementation of technology transfer policies and procedures for the Department of Health and Human Services, and for patenting and licensing activities at the NIH and the Food and Drug Administration. Prior to that, Dr. Freire established and headed the Office of Technology Development at the University of Maryland at Baltimore and the University of Maryland Baltimore County.

Dr. Freire is an internationally recognized expert in technology commercialization. Among her appointments, she is a member of the World Health Organization's Commission on Intellectual Property Rights, Innovation and Public Health (CIPRH) and Time Magazine's Global Health Summit Board of Advisors, and is the Chair of the Working Group for New TB Drugs for the global Stop TB Partnership. Born in Lima, Peru, Dr. Freire trained at the Universidad Peruana Cayetano Heredia. She received a Ph.D. in Biophysics and completed post-graduate work at the University of Virginia and at the University of Tennessee. She has received numerous awards, including the Arthur S. Flemming Award, DHHS Secretary's Award for Distinguished Service and the Bayh-Dole Award.

**Peter Barton Hutt** is a senior counsel in the Washington, D.C. law firm of Covington & Burling specializing in food and drug law. He graduated from Yale College and Harvard Law School and obtained a Master of Laws degree in Food and Drug Law from NYU Law School. Mr. Hutt served as Chief Counsel for the Food and Drug Administration during 1971-1975. He is the co-author of the casebook used to teach food and drug law

throughout the country, and has published more than 175 book chapters and articles on food and drug law and health policy. He teaches a full course on this subject during Winter Term at Harvard Law School and has taught the same course during Spring Term at Stanford Law School. Mr. Hutt has been a member of the Institute of Medicine since it was founded in 1971. He serves on academic, philanthropic, and venture capital advisory boards, and the boards of startup biotechnology companies. He currently serves on the Panel on the Administrative Restructuring of the National Institutes of Health, the Working Group to Review Regulatory Activities within the Division of AIDS of the National Institute of Allergy and Infectious Diseases, and the Board of Directors of the AERAS Global TB Vaccine Foundation.

He was named by The Washingtonian magazine as one of Washington's 50 best lawyers (out of more than 40,000) and as one of Washington's 100 most influential people; by the National Law Journal as one of the 40 best health care lawyers in the United States; and by European Counsel as the best FDA regulatory specialist in Washington, D.C. In June 2003, Business Week referred to Mr. Hutt as the "unofficial dean of Washington food and drug lawyers." In naming Mr. Hutt in September 2005 as one of the eleven best food and drug lawyers, the Legal Times also referred to him as "the dean of the food-and-drug bar." In April 2005, Mr. Hutt was presented the FDA Distinguished Alumni Award by FDA Commissioner Crawford. In May 2005, he was given the Lifetime Achievement Award by the Foundation for Biomedical Research, for research advocacy.

**Gary Schoolnik** is Professor of Medicine, Microbiology and Immunology at Stanford School of Medicine and Attending Physician in Internal Medicine and Infectious Diseases at Stanford University Hospital. For more than 25 years he has worked on infectious diseases that disproportionately affect persons living in developing countries. He currently directs projects in Bangladesh, India and China and has worked extensively in Mexico. He is a member of the Board of Scientific Counselors of Fudan University in Shanghai and a member of the National Advisory Council of the United States National Institute of Allergy and Infectious Diseases. He directs the Tuberculosis Genomic Core facility for the Grand Challenges in Global Health program of the Bill and Melinda Gates Foundation.